

#15
Ratification
of
#13/B**Marked up version of Supplemental Amendment filed January 7, 2003**

1. A human monoclonal antibody or fragment thereof that specifically binds to human CD40.
3. The human monoclonal antibody of claim 1, wherein the antibody is produced by a hybridoma cell line or subclones thereof, and wherein the antibody is denoted as no. 11 or 72, or the hybridoma is denoted as F1-102, F5-152, F2-103, F5-77, F5-157 or F4-465.
4. The human monoclonal antibody of claim 1, wherein the antibody has the CD40 binding specificity of the antibody denoted as no. 11 or 72, or the antibody produced by the hybridoma denoted as F1-102, F5-152, F2-103, F5-77, F5-157 or F4-465.
5. The human monoclonal antibody of claim 1, wherein the antibody has a CD40 modulating activity of the antibody denoted as no. 11 or 72, or the antibody produced by the hybridoma denoted as F1-102, F5-152, F2-103, F5-77, F5-157 or F4-465.
6. The human monoclonal antibody fragment of claim 1, wherein the fragment comprises an scFv, Fab, Fab', or F(ab')₂ fragment.
7. The human monoclonal antibody fragment of claim 6, wherein the fragment comprises a fragment of the antibody denoted as no. 11 or 72, or the antibody produced by the hybridoma denoted as F1-102, F5-152, F2-103, F5-77, F5-157 or F4-465.
8. The human monoclonal antibody of claim 1, wherein the antibody is detectably labeled.
10. The human antibody of claim 1, wherein the antibody decreases binding of a CD40 ligand to CD40.
11. The human monoclonal antibody of claim 1, wherein the antibody increases binding of a CD40 ligand to CD40.
12. The human monoclonal antibody of claim 1, wherein the antibody decreases a CD40 activity.
13. The human monoclonal antibody of claim 12, wherein the antibody contains a lambda light chain sequence.
14. The human monoclonal antibody of claim 12, wherein the antibody decreases proliferation of a cell expressing CD40.
15. The human monoclonal antibody of claim 14, wherein the cell is a B-cell.

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16. The human monoclonal antibody of claim 12, wherein the antibody decreases expression of a protein.
17. The human [anti-CD40] monoclonal antibody of claim 16, wherein the protein comprises CD95, CD80 or CD86.
18. The human monoclonal antibody of claim 1, wherein the antibody increases a CD40 activity.
19. The human monoclonal antibody of claim 18, wherein the antibody increases proliferation of a cell expressing CD40.
20. The human monoclonal antibody of claim 19, wherein the cell is a B-cell.
21. The human monoclonal antibody of claim 18, wherein the antibody increases expression of a protein.
22. The human monoclonal antibody of claim 21, wherein the protein comprises CD95, CD80 or CD86.
23. The human monoclonal antibody of claim 1, further comprising a pharmaceutical formulation.
24. A host cell that expresses the antibody of claim 1.
25. A nucleic acid that encodes the antibody of claim 1.
26. A host cell containing the nucleic acid of claim 25.
27. A method of producing a human CD40 antibody that modulates an activity of CD40 comprising:
 - (a) administering CD40 or an immunogenic fragment thereof to a mouse capable of expressing human immunoglobulin;
 - (b) screening the administered mouse for expression of a human CD40 antibody;
 - (c) selecting a mouse that produces a human CD40 antibody;
 - (d) isolating an antibody from the mouse that produces a human CD40 antibody; and
 - (e) determining whether the human CD40 antibody modulates an activity of CD40 thereby producing a human CD40 antibody that modulates an activity of CD40.
28. A method of producing a human CD40 monoclonal antibody that modulates an activity of CD40; comprising:

- (a) administering human CD40 or an immunogenic fragment thereof to a mouse capable of expressing human immunoglobulin;
 - (b) isolating spleen cells from the mouse that produces a human CD40 antibody;
 - (c) fusing the spleen cells with a myeloma cell to produce a hybridoma; and
 - (d) screening the hybridoma for expression of a human CD40 antibody that modulates an activity of CD40 thereby producing a human monoclonal CD40 antibody that modulates an activity of CD40.
29. A monoclonal antibody isolated from a hybridoma produced by the method of claim 28.
62. The human monoclonal antibody or fragment of claim 1, wherein the antibody inhibits CD95 expression of Ramos B cells mediated by CD40 ligand in vitro, in the condition of 1 $\mu\text{g/ml}$ of soluble CD40 ligand and 1 $\mu\text{g/ml}$ of the antibody.
63. The human monoclonal antibody or fragment of claim 1, wherein the antibody inhibits human B-cell proliferation mediated by CD40 ligand in vitro, in the condition of 1 $\mu\text{g/ml}$ of soluble CD40 ligand and 10 nanogram/ml of the antibody.
64. The human monoclonal antibody or fragment of claim 62 or 63, wherein the antibody has a Kd value of 0.8 to 4 nM, as determined by BiaCore[®] analysis.